REMARKS:

I. Amendments to the claims

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

Claims 1-27 are requested to be cancelled.

Claims 28-50 are being added. The new claims do not add new matter.

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented on pages 3-5, with an appropriate defined status identifier.

Support for the new claims can be found in the claims and specification as originally filed, including but not limited to the following:

Claim	Claims as originally filed	Specification paragraph number
Claim 28	1, 6	[0008], [0009], [0010], [0025]
Claim 29		[0013]
Claim 30	7	[0013]
Claim 31	8	[0013]
Claim 32	17	[0013]
Claim 33	4	[0013]
Claim 34	5	[0044]
Claim 35	4	[0033], [0034]

Claim 36	4	[0035]
Claims 37-38	12, 13	[0035], [0071], [0071]
Claim 39	14	[0033], [0034]
Claim 40	15	[0058], [0059]
Claim 41	16	[0066]
Claim 42	19	[0026]
Claim 43		[0031]
Claim 44		[0032]
Claim 45	18	[0032], [0045]
Claim 46	1, 6	[0008], [0009], [0010]
Claim 47	3	[0025]
Claim 48	8,17	[0033], [0034], [0035]
Claim 49		[0009]
Claim 50	19	[0027]

After amending the claims as set forth above, claims 28-50 are now pending in this application.

II. Claim objection

Claim 13 is objected to as allegedly "being dependent on non-elected claim 11." (Office Action at 2). Claim 13 has been cancelled thereby obviating the objection. As such, reconsideration and withdrawal of the objection is respectfully requested.

III. Claim rejections – 35 U.S.C. § 112, second paragraph

Claims 2-5, 9, 26 and 27 are rejected under 25 U.S.C. § 112, second paragraph allegedly as being indefinite. (Office Action at 2.) Applicants respectfully traverse the rejection.

Claims 2-5, 9, 26 and 27 have been cancelled thereby obviating the rejection. New claims 28-50 are clear, and the language suggested by the Office Action has been incorporated where appropriate. As such, the new claims meet the requirements of 35 U.S.C. § 112 second paragraph, and reconsideration and withdrawal of the rejections is respectfully requested.

IV. Claim rejections – 35 U.S.C. § 112, first paragraph

Claims 1-9, 12-19 and 26 and 27 are rejected under 25 U.S.C. § 112, first paragraph allegedly, because "the specification, while being enabling for a method of inducing immune tolerance to carbohydrate antigens in mice ... does not reasonably provide enablement for a method of inducing immune tolerance to any antigen in any mammals...." (Office Action at 3). Applicants respectfully traverse the rejection.

Claims 1-9, 12-19 and 26 and 27 have been cancelled thereby obviating the rejection. New claims 28-50 are directed to the use of carbohydrate antigens to induce immune tolerance in a mammal and these claims fully comply with the requirements of 35 U.S.C. §112, first paragraph for at least the following reasons: A) the application enables the claimed methods with carbohydrate antigens; and B) the application enables the claimed methods for use in other mammals, including humans.

A. The application enables the claimed methods with carbohydrate antigens.

The Office Action asserts that a showing of immune tolerance to a particular carbohydrate antigen in mice does not enable a method of "inducing immune tolerance to any

antigen in any mammals." (Office Action at 3). In support of this, the Office Action asserts that "no animals were used as model systems to effectively induce immune tolerance to any antigen...." (Office Action at 5). Additionally, the Office Action asserts that "carbohydrate antigens on glycoproteins differ from peptide antigens in that they cannot activate T cells directly because of their protrusion from MHC groove," and that "[t]herefore incompatible carbohydrate antigens on syngeneic cells cannot activate T cells." (Office Action at 4, citing Ogawa *et al.*, Blood 2003, 101:2318-2320).

First, new claims 28-50 do not relate to inducing immune tolerance to "any antigen in any mammal," rather, the claims relate to inducing immune tolerance to carbohydrate antigens against which the mammal is not naturally tolerant. For example, the methods do not encompass inducing immune tolerance in a human of blood type B against blood type B antigens; nor do the methods include inducing α-Gal tolerance in a mammal (*e.g.*, a horse, pig or cow) which is already immune tolerant to the α-Gal antigen. Additionally, as noted by the Office Action, the specification includes detailed explanations and experimental examples using an exemplary carbohydrate antigen, the α-Gal antigen, to teach induction of immune tolerance in a mammalian model system, mice, because "[m]ice are the experimental tool of choice for the majority of immunologists," Mestas *et al.*, J. Immunology, 2004, 172:2731-38. The mice used to demonstrate the methods of the present invention were not naturally immune tolerant to the α-Gal carbohydrate antigen (Specification at page 18, paragraph [0052]).

Second, recent work by the inventors demonstrates that immune tolerance to another carbohydrate antigen, the B blood group antigen, can be induced using the methods of the present invention. As presented in the accompanying declaration by Dr. Uri Galili (Galili Declaration), the tolerance to the B blood group antigen was induced in the mouse model system, and was accomplished using the methods of the present disclosure using no more than routine experimentation. (*see* Galili Declaration at ¶ 5).

A brief background to the experiment is presented. Similar to the α-Gal epitope, development of the different human ABO blood groups requires specific transferases to create

the specific carbohydrate antigens. For example, in a blood group B subject, the B transferase modifies the H antigen, which is the "acceptor" substrate for blood group carbohydrate modifications, by adding the specific B blood group antigen to the H antigen. Likewise, in a blood group A subject, the A transferase modifies the H antigen with the specific A blood group antigen. The human blood group O transferase is non-functional, therefore in a blood group O subject, the H antigen remains unmodified.

In the experiment presented in the declaration, spleen lymphocytes were isolated from Balb/c mice and nucleofected with two expression vectors, one carrying the human H transferase gene and one carrying the B transfease gene. (Galili Declaration at ¶ 6). Thus, these cells can produce both the substrate (H antigen) and the epitope (B antigen). Control lymphocytes were transduced with mock vector. (*Id.* at ¶ 7). The transduced cells were then administered to syngeneic mice. (*Id.* at ¶ 7). Cell administration was repeated four more times in 3-4 day intervals. (*Id.*) Subsequently, the mice were intraperitoneally immunized with human blood type B antigen a total of four times at two week intervals. (*Id.* at ¶ 8). Two weeks after the last immunization, the mice were tested for anti-B antibody production. (*Id.* at ¶ 9).

Mice which received lymphocytes expressing both the H and B transferase produced significantly lower amounts of anti-B antibodies than mice which received only the B transferase or the mock vector alone. (*Id.* at ¶¶ 11, 12). This example further demonstrates that the claimed methods of inducing immune tolerance to carbohydrate antigens are fully supported by the specification.

Third, the difference between some carbohydrate antigens and peptide antigens in their ability to activate T-cells is capitalized upon in the present invention and can not be construed, in any way, to be non-enabling. Indeed, it is hypothesized that because certain carbohydrate antigens cannot directly activate T-cells and incite T-cell help, the methods of the present invention induce immunotolerence so effectively. For example, the specification at page 4 notes, "[t]he basis for tolerance is believed to be that in the absence of any T cell help, the cross linking of B cell receptors by the cognate carbohydrate antigen on autologous cells results in

tolerance induction on the B cell." (Specification at 4, paragraph [0013]). Such carbohydrate antigens are described at page 14, paragraph [0041], as having "a size similar to the size of a 25-30 amino acid peptide," and include, but are not limited to carbohydrate antigens such as the ABO blood group antigens and the α-Gal antigen.

Thus, the specification provides sufficient teaching such that one skilled in the art can use the methods of the present invention to induce immune tolerance to a carbohydrate antigen in a mammal without undue experimentation. First, the specification describes, in detail, methods to generate immune tolerance in a model mammalian system against a carbohydrate to which the mammal is not naturally immune tolerant. Second, recent data demonstrates the generation of immune tolerance against a completely different carbohydrate. The immune tolerance was generated using the methods of the present invention and was accomplished without undue experimentation. Third, the observation that certain carbohydrates do not activate T-cells supports rather than undermines enablement of the present invention.

B. The application enables the claimed methods in other mammals, including humans.

As describe above, new claims 28-50 are directed to carbohydrate antigens, not "any antigen," and the specification fully enables the claimed methods using such antigens.

In addition, the specification provides ample teachings to enable one of skill in the art to understand how induce immune tolerance to carbohydrate antigens in mammals other than mice, including humans, without undue experimentation.

First, mice are recognized by those skilled in the art as the model of choice for human immunological research. Indeed, the very reference cited by the Office Action, Mestas *et al.*, states that "[m]ice are the experimental tool of choice for the majority of immunologists and the study of their immune responses has yielded tremendous insight into the workings of the immune system," and that "[m]ice are the mainstay of in vivo immunological experimentation and in many respects they mirror human biology remarkably well." Mestas *et al.*, J. Immunology, 2004,

172:2731-38. Additionally, Mestas *et al.* note that "[i]n this review our aim is not to suggest that the mouse is an invalid model system for human biology," and that "[w]hile caution in interpreting preclinical data obtained in mice is clearly warranted, we believe that with these caveats in mind mice will continue to be the premiere *in vivo* model for human immunology and will be absolutely essential for continued progress in our understanding of immune system function in health and disease." *Id.* Accordingly, although the reference describes some of the difference between mice and humans and expresses the need for *caution* in interpreting preclinical data derived from mice, the reference also acknowledges that mice are the model of choice for human immunological research. One of skill in the art would understand this, and would also understand how to extrapolate the information presented in the current application and apply it to other mammals, including humans.

Second, data from the KO mouse model can be correlated to other mammals, including humans. The Office Action incorrectly describes human immunotolerance with respect to α-Gal antigen. The Office Action asserts that "most mammals, including human are immunologically tolerant to α-Gal because their immune system develops in the environment that recognizes this antigen as 'self.'" (Office Action at 4). This is incorrect. Most mammals, except humans, apes and Old World monkeys are immunologically tolerant to α-Gal (*see* Ogawa *et al.*, Gene Therapy 2004, 11:292-301, at 292, cited in the Office Action; *see also* Bracy *et al.*, Blood 2000, 96(9):3008-3015, cited in the Office Action and stating that "[a]ll placental mammals except humans, apes and Old World monkeys ... are immunologically tolerant to αGal"). Thus, humans, like the KO mice, are not immunologically tolerant to α-Gal. As such, one of ordinary skill in the art would be able to correlate the data and results obtained with the α-Gal/KO mouse model system to results that may be obtained using other carbohydrate antigens and non-immunologically tolerant mammals, including humans.

Third, the carbohydrate antigens of the present invention can be expressed on other mammalian cells; testing in monkeys is not necessary to establish the relevance of the methods. In fact, the specification describes use in other mammals, specifically humans, for example at

paragraphs [0033] – [0034] (transplantation of ABO mismatched allograft), and at paragraphs [0035] – [0036] (transplantation of human patients with a xenograft). Additionally, experimental examples using HeLa cells (an immortalized human cell line) are provided at paragraph [0045] and paragraph [0061]. These examples demonstrate that a carbohydrate antigen (*e.g.*, α-Gal) can be expressed by the methods of the present application, on the surface of a human cell. Also, as discussed above, data submitted herewith demonstrates that a human blood antigen (B-blood group antigen) can be expressed on the surface of a mammalian (*e.g.*, mouse) white blood cell, and that when the cells expressing the antigen are introduced into mice according to the methods of the present invention, immune tolerance to the antigen is induced in these mice. (Galili Declaration).

Accordingly, the specification provides sufficient teaching such that one skilled in the art can use the methods of the present invention to induce immune tolerance to a carbohydrate antigen in other mammals, including humans, without undue experimentation. First, mice are the model system for immunological studies in mammals, including humans, and correlating immunological data from mice to other animals is well known and understood by those skilled in the art. Second, immunotolerance data from the KO mouse model system can be correlated and extrapolated to other carbohydrate antigens in other immunoreactive mammals, including humans, because the KO mice are not immunotolerant (*i.e.*, are immunoreactive) to the α-Gal antigen. Third, data in the specification and recent findings show that carbohydrate antigen can be expressed in human cells and that human antigens can be expressed in mammalian (*e.g.*, mouse) white blood cells to induce immune tolerance.

For at least the reasons provided above, reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph is respectfully requested.

V. Claim rejections – 35 U.S.C. § 102(e)

Claims 1-4, 9, 12-16 and 19 are rejected under 35 U.S.C. 102(e) as allegedly being anticipated by U.S. 2002/0119571 (the '571 application) or WO 01/079300 (the '300 application). Applicants respectfully traverse the rejection.

As noted in the Manual of Patent Examining Procedure ("MPEP"), "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference," and "'[t]he identical invention must be shown in as complete detail as is contained in the ... claim." (MPEP §2131, 8th ed. Rev. 3 Aug. 2005). Further, "[a] claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers." (35 U.S.C. §112, paragraph 4).

Claims 1-4, 9, 12-16 and 19 have been cancelled thereby obviating the rejection. New claims 28-50 are not anticipated by the '571 application or the '300 application under 35 U.S.C. 102(e) because each element of the claims is not present in the prior art references for the reasons that follow.

A. U.S. 2002/0119571 does not anticipate claim 28 or claim 46 because each and every element of the claims is not present in the reference.

The present application distinguishes over the '571 application at least by reciting that the population of engineered white blood cells administered to the mammal express a carbohydrate antigen, thereby inducing at least partial immune tolerance to the antigen in the mammal. By contrast, the '571 application lacks any disclosure related to carbohydrate antigens but instead relates to "in-vitro gene-modified T cells for the prevention of allogeneic transplant rejection in-vivo, a process for their production and their use." ('571 application at [0002]).

Specifically, the '571 application describes the use of transduced T-cells to produce therapeutic gene products, for example, cytokines. The T-cells transduced with the cytokine may then secrete the therapeutic gene product (*e.g.*, interleukins). The interleukins then act to "modulate Th1-mediated immune reactions" to "promote prolonged graft acceptance," (*see e.g.*,

'571 paragraphs [0006], [0014], [0027] and [0029]). Thus, the '571 application describes a method to produce therapeutic gene products, such as cytokines (*e.g.*, IL-10, IL-4 and IL12p40; *see* '571 paragraphs [0042]), via a transduced T-cell. The therapeutic gene products, however, are not expressed as foreign carbohydrate antigens to be contacted by B-cell receptors to induce immune tolerance to that same carbohydrate antigen.

The '571 application also lists genes whose products may be expressed on the cell surface (*see* '571 application, paragraph [0039] listing CTLA-4, hSerrate, hDelta1 and Notch1-4 family members); however, these gene products are not carbohydrate antigens which contact B-cell receptors, and their expression does not confer immunotolerance to themselves. CTLA-4, for example, which is expressed transiently on activated T-cells, appears to be important in negative regulation of T cell responses generally. (*See e.g.*, WO 01/79300 at page 2, lines 20-23). Similarly, expression of the other gene products on cell surfaces may act to generally affect the T-cell immune response as well. (*See e.g.*, Hoyne, J. Leukocyte Biology, 2003 74:971-981, submitted herewith in the accompanying IDS) This, however, is not the same, and does not does not constitute a description of the expression of a carbohydrate antigen on a white blood cell to induce immune tolerance to that particular antigen. In the '571 application, the transduced gene products are valued for their function as cytokines, general mediators of T-cell response, or for their ability to protect the cell in which they are expressed, but they are not used as antigens.

As such, each and every element as set forth in claim 28 and 46 is not found, either expressly or inherently, in the '571 application. Accordingly, the '571 application does anticipate claim 28 or 46 or claims depending therefrom.

B. WO 01/079300 does not anticipate claim 28 or claim 46; each and every element of the claims is not present in the reference.

The '300 application relates to the expression of an antibody on a cell surface, where the antibody is capable of binding CTLA-4 or CD28. However, the '300 application does not describe a carbohydrate antigen expressed on a white blood cell and the induction of immunotolerance to that specific carbohydrate antigen.

In the '300 application, CTLA-4 is described as being transiently expressed on activated T-cells. Likewise, CD28 is described as being constitutively expressed in resting T-cells, although expression of CD28 increases with T-cell activation, ('300 application at page 2, lines 20-23; page 1, line 30). According to the methods of the '300 application, the cell-surface antibody would bind to CTLA-4 or CD28. Binding of CTLA-4 by the appropriate antibody results "in downmodulating the immune response," ('300 at 51, lines 26-28, emphasis added), while binding of CD28 by the appropriate antibody results in "enhancing the immune response" ('300 application at 54, lines 16-18, emphasis added). Thus CD28 binding has the exact opposite effect produced by the current methods which induce immune tolerance. While the '300 application describes the expression of a CTLA-4 binding antibody on the surface of a cell which acts to downmodulate the immune response, this is not the same and does not constitute a description of expressing a carbohydrate antigen on a white blood cell and inducing immune tolerance to the carbohydrate antigen.

Accordingly, each and every element as set forth in claim 28 and 46 is not found, either expressly or inherently, in the '300 application; thus, the '300 application does anticipate claim 28 or 46 or claims depending therefrom.

In summary, neither the '571 application nor the '300 application describe each and every element as set forth in independent claims 28 and 46 "in as complete detail as is contained in the ... claim." (MPEP §2131). Reconsideration and withdrawal of the rejections under 35 U.S.C. § 102(e) is respectfully requested.

VI. Claim rejections – 35 U.S.C. § 103(a)

Claims 1-9 and 17-19 and 26 and 27 are rejected under 35 U.S.C. § 103 as allegedly being unpatentable over U.S. 2002/0119571 (the '571 application) or WO 01/079300 (the '300 application) in view of U.S. Patent No. 5,879,675 (the '675 patent). Claims 1-9, 12-19 and 26

and 27 are rejected under 35 U.S.C. § 103 as allegedly being unpatentable over Bracy *et al.*, (Blood 2000, 96:3008-3015) in view of the '571 application and the '675 patent. Applicants respectfully traverse these rejections.

Claims 1-27 have been cancelled, thereby obviating the rejections. Applicants respectfully submit that new claims 28-50 are not obvious in light of the cited references because a prima facie case of obviousness has not been established.

In order to establish a *prima facie* case of obviousness:

> ...three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. M.P.E.P. § 2143.

Moreover, it should be noted that, "the proposed modification cannot render the prior art unsatisfactory for its intended purpose." (MPEP § 2143.V). Finally, if an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is nonobvious." (MPEP § 2143.03).

A. The prior art references U.S. 2002/0119571 or WO 01/079300 in view of U.S. Patent No. 5,879,675 fail to establish a prima facie case of obviousness.

The Office Action asserts that "U.S. Patent 2002/0119571 or WO 01/079300 does not explicitly teach a method of inducing immune tolerance to an carbohydrate antigen," but that U.S. Patent '675 teaches a method of engineering a population of cells expressing α-Gal epitope on its surface, comprising transducing said cells with replication defective adenovirus containing α 1,3 GT gene," and that U.S. Patent '675 teaches that "said engineered cells can be used to target immune response in mammals." (Office Action at 6). The Office Action further asserts that "it would have been obvious for one of ordinary skill in the art ... to apply the teaching of U.S. Patent '675 to those of U.S. Patent 2002/0119571 or WO 01/079300 to obtain a claimed

method of inducing immune tolerance to a carbohydrate antigen ... wherein engineered population of white blood cells are obtained by inserting the nucleic acid encoding said antigen by replication defective adenovirus." (*Id.*)

Applicants respectfully traverse this rejection because the cited references do not teach or suggest all the limitations of claim 28 or 46 and there is no motivation to combine or modify the references.

1. The references do not teach or suggest all the limitations of claims 28 and 46.

As described above in Section V and as admitted by the Examiner on page 6 of the Office Action, neither the '571 application nor the '300 application teach inducing immune tolerance to a carbohydrate antigen. Each reference describe methods to generally suppress the immune system such as transiently expressing CTLA-4 on T-cells but does not teach or suggest inducing immune tolerance to a specific antigen. In particular, neither reference teaches or suggests inducing immune tolerance in a mammal to a carbohydrate antigen by expressing the carbohydrate antigen on white blood cells administered to the mammal. The '675 patent fails to cure these deficiencies.

In fact, the '675 patent teaches methods having the exact opposite effects of the immune tolerance produced by the claimed methods. The '675 patent discloses methods which generally enhance the immune response to specific, tumor-associated antigens by improving phagocytosis (opsonization) of the tumor-associated antigen ("TAA"). ('675 col. 2, lines 38-40). The TAA is opsonized via its proximity to α-Gal epitope ('675 col. 2, lines 49-51) in an "α-galactosyl epitope containing complex, which complex includes the antigen and a lipid bilayer." ('675 col. 2, lines 58-60). The '675 patent also describes enhancing opsonization of viruses by expressing a viral subunit on a cell surface along with an α-gal epitope. Again, however, this is directed to enhancing the immune response, not inducing tolerance. (*See* '675 col. 8, lines 62-66, col. 9 lines 1-18). Moreover, the COS-1 cells engineered to express α1,3 galactosyltransferase enzyme were not used to express the α-gal epitope in order to target the immune response as asserted in the

Office Action. Instead, the expressed α1,3 galactosyltransferase was isolated and used for the *in vitro* biochemical addition of the α-galactosyl epitope to viral and tumor cell surfaces (*Id.* at col. 22, line 7 – col. 24, line 17 and col. 25, lines 1-32). None of these examples can be construed to fairly suggest expressing a carbohydrate antigen on a white blood cell to induce immune tolerance to a carbohydrate antigen. Accordingly, the '675 patent alone or in combination with the other cited art not only lacks all of the elements of the claimed methods, but teaches away from the present methods.

2. There is no motivation to combine the cited references: The proposed modification would render the prior art unsatisfactory for its intended purpose.

Modifying either U.S. Patent 2002/0119571 or WO 01/079300 according to the teachings of U.S. 5,879,675 would render the inventions of both references unsatisfactory for their intended purpose. As such, one of skill in the art would not be motivated to combine these reference.

The '571 application describes the use of transduced T-cells to produce therapeutic gene products, for example, cytokines to "modulate Th1-mediated immune reactions" to "promote prolonged graft acceptance." (*See e.g.*, '571 paragraphs [0006], [0014]). Thus, the '571 application describes methods to generally down modulate T-cell mediated immune response. Similarly, the '300 application relates to the expression of an antibody on a cell surface, where the antibody is capable of binding CTLA-4 or CD28. Binding of CTLA-4 by the appropriate antibody results "in down modulating the immune response," ('300 at 51, lines 26-28). Conversely, U.S. Patent '675 teaches methods to generally enhance the immune response to specific, tumor-associated antigens and tumor cells by improving phagocytosis (opsonization) of the tumor-associated antigen ("TAA"). ('675 column 2, lines 38-40). Accordingly, to modify the "down modulating" methods described in the '571 application or the '300 application according to the "immuno-enhancing" teachings of '675 would render the methods of these references non-functional–and unsatisfactory–for their intended purpose. As such, the teachings of the cited art may not be combined or modified with the other cited references, and there can be no reasonable likelihood of success in such a combination or modification.

Finally, because none of these references teach or suggest that white blood cells may be used to generate immune tolerance to a carbohydrate antigen, and because the '675 actually teaches away from the present methods, Applicants believe that it is only via impermissible hindsight that these references were identified at all (*see e.g.*, MPEP § 2141.II.C, stating "[t]he references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention....").

Accordingly, Applicants respectfully submit that the cited references, alone or in combination do not teach or suggest expression of a carbohydrate antigen on a white blood cell for the purposes of inducing immune tolerance to that antigen. As such, the subject matter of the claimed invention, as a whole, would not have been obvious to one of ordinary skill in the art. Reconsideration and withdrawal of the rejection under 35 U.S.C. §103 over U.S. 2002/0119571 or WO 01/079300 in view of U.S. Patent No. 5,879,675 is respectfully requested.

B. The prior art references Bracy in view of 2002/0119571 and U.S. 5,879,675 fail to establish a prima facie case of obviousness.

The Office Action asserts that it would have been obvious to apply the teachings of the '571 application and U.S. '675 to those of Bracy *et al.* to obtain the claimed methods. (Office Action at 8.) Applicants respectfully traverse this rejection. The cited references do not teach or suggest all the claimed limitations and there is no motivation to combine the cited references.

As described above in Section VI A, neither the '571 application nor the '675 patent teach or suggest inducing immune tolerance to a carbohydrate antigen. The '571 application describes the use of transduced T-cells to produce therapeutic gene products, e.g., cytokines, to "modulate Th1-mediated immune reactions" to "promote prolonged graft acceptance." The '675 patent teaches methods to generally enhance the immune response to specific, tumor-associated antigens by improving phagocytosis (opsonization) of the tumor-associated antigen ("TAA") by placing the TAA antigen in close proximity to the α-gal epitope ('675 column 2, lines 38-40). Thus, the '675 patent teaches away from the present disclosure.

Likewise, and as admitted in the Office Action (p. 8), Bracy *et al.* do not teach transduction via a replication defective adenovirus to express a carbohydrate antigen on a white blood cell in order to induce immune tolerance in a mammal. Rather, Bracy *et al.* teach the use of a retrovirus to transduce bone marrow cells to induce tolerance to the α-Gal epitope in KO mice. Contrary to the Office Action assertion that "Bracy *et al.*, do not limit their studies to use only engineered BM cells," no other cells are taught or suggested for transduction and expression of a carbohydrate antigen. (*See, e.g.*, Bracy *et al.* at 3013: "We hypothesized that it may be possible to utilize gene therapy to inhibit production of αGal XNA by introducing a functional αGT gene via retroviral gene transfer into bone marrow cells.") Should the Examiner disagree, Applicants respectfully request that the Examiner identify in Bracy *et al.* exactly where the use of other cells are suggested so that Applicants may respond more fully to this argument.

Thus, none of the cited references, alone or in combination teach or suggest the transduction of a white blood cell to induce immune tolerance to a carbohydrate antigen. Even if the cited references did teach each of the elements, modifying either Bracy or U.S. 2002/0119571 according to the teachings of U.S. 5,879,675 would render the inventions of both references unsatisfactory for their intended purposes. As such, one of skill in the art would not be motivated to combine or modify these reference or assured of a reasonable likelihood of success in doing so.

The '571 application describes the use of transduced T-cells to produce therapeutic gene products, for example, cytokines to "modulate Th1-mediated immune reactions" to "promote prolonged graft acceptance." (*See e.g.*, '571 paragraphs [0006], [0014]). Thus, the '571 application describes methods to generally down modulate T-cell mediated immune response. Bracy *et al.* describe a method to transduce bone marrow cells to induce immune tolerance to an antigen, thereby "down modulating" the immune response with respect to that antigen. Conversely, U.S. Patent '675 teaches methods to generally enhance the immune response to specific, tumor-associated antigens by improving phagocytosis (opsonization) of the tumor-associated antigen ("TAA"). ('675 column 2, lines 38-40). Accordingly, to modify the "down

modulating" methods described in the '571 application or in Bracy *et al.* according to the "immuno-enhancing" teachings of '675 would render the methods of these references non-functional for their intended purpose.

Additionally, the Office Action makes the unsupported assumption that the transduction of white blood cells, rather than bone marrow cells, to induce immune tolerance to a carbohydrate antigen would have been obvious in light of the teachings of Bracy, the '571 application and the '675 patent. In fact, because none of these references teach or suggest that white blood cells may be used to generate immune tolerance to a carbohydrate antigen, and because the '675 actually teaches away from the present methods, Applicants believe that it is only via impermissible hindsight that these references were identified or combined at all (*see e.g.*, MPEP § 2141.II.C, stating "[t]he references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention…").

Moreover, Applicants respectfully submit that copious evidence available at the time of filing of the present application taught away from the use of any cells other than bone marrow cells to generate immune tolerance. For example, at that time, bone marrow transplantation ("BMT") was characterized as "the most promising concept for clinical tolerance induction." (Wekerle *et al.*, Annu. Rev. Med., 2000, 52:353-70, submitted herewith in the accompanying IDS). This characterization was due in part to two factors. First, BMT had been demonstrated to work under a number of different conditions (*see e.g.*, Wekerle *et al.* at 354-55, describing permanent primary skin graft acceptance, long-term acceptance of renal allografts in non-human primates, and the success of human allogeneic BMT followed by lung or kidney transplant; *see also*, Bracy *et al.*, Mol. Ther., 2002, 6(2):252-257; Odha *et al.*, Transplantation, 2000, 71(11):1532-1542; both submitted herewith in the accompanying IDS). Second, BMT maintains "robust tolerance through the well-defined and clinically desirable mechanism of intrathymic clonal deletion of donor-reactive cells." (Wekerle *et al.* at 354). Indeed, establishment of such long term tolerance is important to any successful tolerance protocol (*see* Wekerele at al. at 355).

A key reason BMT can induce such "robust tolerance" is because bone marrow cells include progenitor cells while circulating lymphocytes do not. These progenitor cells function as part of "nature's major mechanism of self-tolerance" (Wekerle *et al.* at 356), as shown in the excerpt below.

> Donor stem cells, which...engraft in the BM compartment of the recipient...where they coexist with recipient stem cells and give rise to cells of all hematopoietic lineages as long as chimerism persists.... Hematopoietic progenitor cells stemming from the BM seed the thymus...giving rise to a specialized subset of cells called thymic dendritic cells...which are effective mediators of intrathymic clonal deletion.... Clonal deletion is the elimination of T cells with a certain antigen specificity.... In the thymus, self-reactive T cells are clonally deleted during their maturation through the physiologic process of negative selection. Antigens expressed on cells of hematopoietic origin within the thymus are the most effective mediators of negative selection.... [T]he newly developing T cell repertoire in mixed chimeras is tolerant toward both the donor and the host.... This tolerant state is maintained for as long as sufficient levels of donor antigen-presenting cells are present in the thymus, which in turn depends on the persistence of adequate numbers of donor hematopoietic stem cells in the BM.
>
> Wekerle et al. at 356.

Critical to this mechanism, donor bone marrow cells will give rise to all hematopoietic lineages–including immune cells–and will also act to seed the thymus, thereby providing a basis for the clonal deletion of donor-specific T-cells. The desire to capitalize on these unique properties of bone marrow cells helped to strongly focus those skilled in the art on bone marrow instead of circulating lympyhocytes to induce and establish immune tolerance.

In contrast to bone marrow cells, circulating lymphocytes are not progenitors of all immune cells, and do not play such a global role in clonal selection and deletion. In particular, because circulating lymphocytes do not include progenitor cells, lymphocytes can not play the same role that bone marrow cells do in establishing and maintaining immune tolerance. Thus, extensive research conducted up to the time of filing focused on bone marrow cells for their

unique ability to produce immuno-tolerant differentiated immune cells, the rank and file actors of the immune system. Members of this rank and file, including circulating lymphocytes, would not have been expected to have the necessary global effect on the immune system to establish long-term tolerance. Thus, Applicants submit that one of ordinary skill in the art would not have had any motivation to attempt to induce immune tolerance using transduced lymphocytes instead of bone marrow cells, and could not have had a reasonable expectation of success.

In summary, because the combined references do not teach each element of the claimed methods and there is no motivation to combine or modify the cited references and no reasonable expectation of success, the subject matter of the claimed invention, as a whole, would not have been obvious to one of ordinary skill in the art. Reconsideration and withdrawal of the rejection under 35 U.S.C. §103 over Bracy *et al.*, in view of 2002/0119571 and U.S. 5,879,675 is respectfully requested.

VII. Conclusion

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. If any issues remain unresolved in view of the present response, the Examiner is invited to contact the undersigned by so that a prompt disposition of the present application may be achieved.

Respectfully submitted,

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By _____

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